

# Epoxidation of Methyl Linoleate. II. The Two Isomers of Methyl 9, 10: 12, 13-Diepoxysearate

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## Abstract

Epoxidation of methyl linoleate results in the formation of two stereoisomeric methyl 9,10:12,13-diepoxysearates. The previously well-known isomer, mp 32°C, represents only 60% of the total diepoxides formed. The newly isolated form is liquid at room temperature and is measured incompletely by standard titrimetric oxirane analysis. The isomers differ by the relative positions of their oxirane oxygen atoms. The oxygens of the solid are located on opposite sides and those of the liquid are on the same side of the molecular plane.

## Introduction

THE EPOXIDATION OF OLEFINS has been studied intensively, and much detailed knowledge has been accumulated (1,2). The conversion of monounsaturated fatty acids and their derivatives to the corresponding oxirane compounds is particularly well understood (3) and usually proceeds in yields exceeding 80% or 90% of theoretical. On the other hand, a great amount of uncertainty and confusion surrounds the epoxidation of linoleic acid and its esters of monohydric alcohols, a reaction which has been reported consistently to proceed in 25–40% yield of isolated product (3–7). One group of authors (8–10) reported that in addition to the usually reported crystalline dioxide (mp 32°C), the oxidation of methyl linoleate also gave rise to an equal amount of liquid isomer. The hydrolysis of the solid diepoxy ester furnished the frequently reported diepoxysearic acid (mp 78°C), while hydrolysis of the liquid ester produced a liquid diepoxysearic acid. The structural relationship of the two materials was not indicated, nor was any evidence presented to support the claim that the liquid product is indeed a single compound.

The purpose of the present paper is to report the isolation and purification of a second isomer of methyl 9,10:12,13-diepoxysearate, a liquid at room temperature, and of the corresponding free acid (mp 41.7°C). Evidence will be presented to demonstrate that both the solid and the liquid methyl esters are 9,10:12,13-diepoxysearates, and that the two differ only in the spatial arrangement of their oxirane oxygens.

## Experimental

### Materials

**Methyl Linoleate.** The material described previously (12) was used.

**Peracetic Acid.** A commercial 40% solution of peracetic acid in acetic acid was analyzed as described below before use.

**Methyl Vernolate.** Prepared from trivernolin as described earlier (12).

### Methods

**Epoxidation of Methyl Linoleate.** To 70.0 g (0.238 moles) of methyl linoleate in 500 ml chloroform was

added 112.0 g of 35.4% peracetic acid in acetic acid (0.521 moles peracetic acid) in which 5.6 g sodium acetate trihydrate had been dissolved. The addition was carried out over a period of 20 min with agitation, while the reaction temperature was controlled at 27–29°C by means of a cooling bath. After addition was complete the reaction mixture was stirred for 3½ hr at room temperature and was then washed successively with 2 × 300 ml water, 300 ml sodium bicarbonate solution (2%), and again with 2 × 300 ml water. The chloroform solution was then dried over CaSO<sub>4</sub> and evaporated to obtain 72.3 g crude oil, oxirane oxygen (13), 9.06% (Theory 9.80%); I.V. 2.23. Yield calculated as methyl diepoxysearate, 86.1% (based on oxirane value).

**Methyl 9,10:12,13-Diepoxysearate, Solid Isomer.** Crude methyl diepoxysearate (70.0 g) was dissolved in 350 ml Skellysolve B and the solution cooled at –30°C to obtain 39.6 g crystalline product, oxirane oxygen, 9.49% (Theory 9.80%). Recrystallization from acetone at –30°C and from petroleum ether (bp 30–60°C) at –2°C gave solid methyl 9,10:12,13-diepoxysearate, mp 32.4–33°C,  $n_D^{20}$  1.4520.

**Anal.** Calc'd for: C<sub>19</sub>H<sub>34</sub>O<sub>4</sub>: C, 69.90; H, 10.50; oxirane oxygen, 9.80; sap. equiv., 326.5.

**Found:** C, 69.99; H, 10.50; oxirane oxygen (14) 9.54; sap. equiv., 328.2.

Gas-liquid chromatographic (GLC) analysis gave a single peak. Liquid isomer and monoepoxides were absent.

**Methyl 9,10:12,13-Diepoxysearate, Liquid Isomer.** Methyl linoleate (100 g, 0.340 moles) was treated with 41.4% peracetic acid solution (138 g, 0.751 moles) as described above. The crude methyl diepoxysearate was dissolved in Skellysolve B and the bulk of the solid isomer removed by crystallization at –30°C (see previous paragraph). The filtrate was concentrated to a liquid residue containing (by GLC analysis) 85.4% methyl diepoxysearates, lesser amounts of monoepoxidized methyl linoleate, traces of methyl linoleate and solvent. The liquid:solid isomer ratio of the diepoxides was approximately 8.3:1.

A portion of the crude liquid isomer mixture (43.9 g) and 132 g urea were dissolved with heating in 440 ml methanol, and the solution was allowed to cool to room temperature. The resulting crystals were collected and were then decomposed in 600 ml water. The aqueous mixture was extracted with 3 × 200 ml ether, and the combined ether extracts were washed with 100 ml water, dried over calcium sulfate and evaporated. The liquid residue (27.6 g) contained 81.8% methyl diepoxysearate having a liquid:solid isomer ratio of 13:1.

The enriched liquid isomer mixture dissolved in benzene was adsorbed on a column of Davison No. 923 silica gel (16 g silica gel per gram of sample). Methyl diepoxysearate, essentially free from impurities, was eluted with benzene-ether mixtures ranging in benzene:ether ratios from 100:1 to 70:1. Fractions having relatively high liquid:solid isomer ratios

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were combined to obtain 7.6 g semipure liquid methyl 9,10:12,13-diepoxysearic acid containing 93.6% liquid isomer and no measurable impurities other than solid isomer. This sample was recrystallized twice from methanol at  $-33^{\circ}\text{C}$  to obtain 4.5 g liquid methyl 9,10:12,13-diepoxysearic acid, purity: 98.8% by GLC (only impurity: 1.2% solid isomer), oxirane oxygen (14) 9.07% (Theory 9.80%).

Another liquid isomer sample, prepared in an analogous manner, had the following constants: mp  $\sim 7.5^{\circ}\text{C}$ ,  $n_D^{20}$  1.4593,  $n_D^{25}$  1.4523.

*Anal.* Calc'd for:  $\text{C}_{18}\text{H}_{34}\text{O}_4$ : C, 69.90; H, 10.50; oxirane oxygen, 9.80; sap. equiv., 326.5.

*Found:* C, 70.02; H, 10.59; oxirane oxygen (13), 8.55; sap. equiv., 328.6.

**9,10:12,13-Diepoxysearic Acid, mp  $78^{\circ}\text{C}$ .** Methyl 9, 10:12,13-diepoxysearic acid, solid isomer (1.0 g), was dissolved in 50 ml 95% ethanol containing 0.33 g KOH, and the solution was heated on the steam bath for 75 min. The mixture was cooled, diluted with 100 ml water, acidified with 85% phosphoric acid and extracted with  $4 \times 25$  ml ether. The ether extracts were combined, washed with  $2 \times 25$  ml water, dried over  $\text{CaSO}_4$ , and evaporated to a solid residue (0.99 g), oxirane oxygen, 9.44% (Theory 10.24%). A portion of the crude solid (0.66 g) was recrystallized twice from acetone to obtain 9,10:12,13-diepoxysearic acid, mp  $78.1\text{--}78.5^{\circ}\text{C}$ .

*Anal.* Calc'd for:  $\text{C}_{18}\text{H}_{32}\text{O}_4$ : C, 69.19; H, 10.33; oxirane oxygen, 10.24; neut. equiv., 312.4.

*Found:* C, 69.20; H, 10.33; oxirane oxygen (13), 9.96; neut. equiv., 315.8.

**9,10:12,13-Diepoxysearic Acid, mp  $41.7^{\circ}\text{C}$ .** Methyl 9,10:12,13-diepoxysearic acid, liquid isomer (1.0 g) was dissolved in 50 ml 95% ethanol containing 0.33 g KOH, and the solution was refluxed for 90 min. The mixture was cooled, diluted with 200 ml water, acidified with 85% phosphoric acid and extracted with  $4 \times 30$  ml ether. The combined ether extracts were washed with  $2 \times 30$  ml water, dried over  $\text{CaSO}_4$  and evaporated to a residual oil (0.91 g). The latter was converted to a solid by adding 10 ml petroleum ether (bp  $30\text{--}60^{\circ}\text{C}$ ) and evaporating the solvent. The product was recrystallized twice from Skellysolve B at

$2^{\circ}\text{C}$  to obtain 9,10:12,13-diepoxysearic acid, mp  $40.8\text{--}41.7^{\circ}\text{C}$ .

*Anal.* Calc'd for:  $\text{C}_{18}\text{H}_{32}\text{O}_4$ : C, 69.19; H, 10.33; oxirane oxygen, 10.24; neut. equiv., 312.4.

*Found:* C, 69.47; H, 10.30; oxirane oxygen (13), 9.00; neut. equiv., 315.6.

**Optically Active Methyl 9,10:12,13-Diepoxysearic Acid, Solid Isomer.** Methyl vernolate (70.0 g) was epoxidized with peracetic acid in the same manner as described for methyl linoleate above to obtain 68.3 g crude methyl 9,10:12,13-diepoxysearic acid. This contained 6% methyl vernolate and 93.8% methyl diepoxysearic acid, the latter having a solid to liquid isomer ratio of about 1.7:1. The crude ester was dissolved in 310 ml Skellysolve B, and after cooling at  $2^{\circ}\text{C}$  overnight, 31.7 g solids were collected. The filtrate was cooled at  $-30^{\circ}\text{C}$  and filtered to collect a second crop of crystals (6.2 g). The second crop filtrate was reserved for isolation of the liquid isomer.

The two crops of solids were combined and recrystallized several times from acetone and from petroleum ether to obtain solid methyl 9,10:12,13-diepoxysearic acid, oxirane oxygen, 9.50;  $[\alpha]_D^{25} = 12.85$  95%  $\text{C}_2\text{H}_5\text{OH}$  ( $c = 10.19$ ). Purity by GLC 99+%.

**Optically Active Methyl 9,10:12,13-Diepoxysearic Acid, Liquid Isomer.** The second crop filtrate from which the solid isomer has been crystallized was evaporated to an oily residue (27.3 g) containing 82.7% methyl diepoxysearic acid (liquid:solid isomer ratio 8:1) and 17.3% methyl vernolate. The residue was chromatographed on silica gel, and a portion of the pure diepoxide fraction eluted with benzene/ether (100:1) was separated. The sample (8.7 g) was complexed with urea as described above for the liquid isomer from methyl linoleate (sample to urea to methanol ratio = 1:3:10). The crystalline complex was collected and decomposed in water, and the contained diepoxide was again complexed. The methyl diepoxysearic acid which was isolated in this manner (2.7 g) had a liquid to solid isomer ratio of 20:1. This material was crystallized from methanol at  $-38^{\circ}\text{C}$  to obtain liquid methyl 9,10:12,13-diepoxysearic acid,  $[\alpha]_D^{25} = -0.77$  95%  $\text{C}_2\text{H}_5\text{OH}$  ( $c = 10.19$ ). Purity by GLC, 98% (solid isomer = 2%).

**Analysis of Peracetic Acid.** The following procedure is suitable for determining the amounts of peracetic acid and of hydrogen peroxide present in solutions of peracetic acid in acetic acid. Analogous methods have been described (2,25).

A sample (0.3–0.4 g) of the peracetic acid solution is weighed accurately into a stoppered 250 ml flask and diluted with 50 ml of 4N aqueous sulfuric acid which had been cooled to  $0^{\circ}\text{C}$ . Saturated potassium iodide solution (3 ml) is added, and the solution is titrated rapidly with 0.1N sodium thiosulfate to a starch-iodide endpoint. This titration measures both peracetic and hydrogen peroxide, and the thiosulfate titer is expressed as percent peracetic acid.

A second sample (0.3–0.4 g) of the peracetic acid solution is weighed accurately into a stoppered 250 ml flask and diluted with 50 ml 4N aqueous sulfuric acid solution which has been cooled to  $0^{\circ}\text{C}$ . The sample is titrated rapidly with 0.1N potassium permanganate to a pink endpoint while being cooled continuously in an ice-salt bath. The permanganate titer, which measures the amount of hydrogen peroxide present, is calculated as percent peracetic acid. The latter figure is subtracted from the percent peracetic acid determined by thiosulfate titration. The differ-

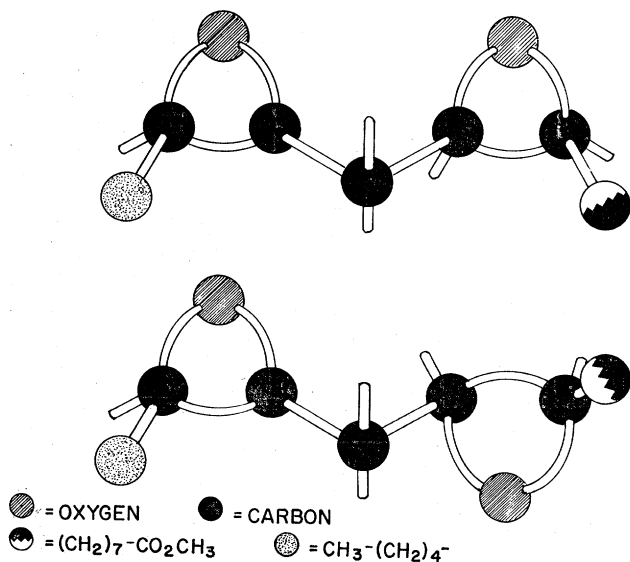


Fig. 1. Positions of the oxirane oxygen atoms in the isomeric methyl 9,10:12,13-diepoxysearic acids.

ence represents the actual amount of peracetic acid present.

**Gas-Liquid Chromatography.** GLC analyses were performed with an apparatus designed at this laboratory. The dual column instrument was provided with a four-filament conductivity cell detector and a recorder having a 1 mV, 1 sec. full-scale pen deflection. The columns were stainless steel coiled tubes, 2 ft  $\times$   $\frac{3}{16}$  in. O.D. (I.D. = 0.118 in.), packed with 60–80 Diatoport coated with 15% XE-60 nitrile silicone. The columns were heated isothermally at 204C, and helium was used as carrier gas. The areas under the peaks were determined by an electronic integrator coupled to a digital printer.

### Discussion

Since a carbon-carbon double bond is a planar structure which can be approached by the epoxidizing agent from either side with equal probability, the epoxidation of an unsymmetrically substituted olefin normally leads to a racemic mixture of *d* and *l* isomers (15). Methyl 9,10-epoxystearate is a case in point. Olefins having two double bonds, e.g. methyl linoleate, are expected to lead to a more complex mixture of isomers.

It has been pointed out (12) that the epoxidation of methyl linoleate occurs with essentially equal ease at the 9,10- and the 12,13-double bond. Each of the two synthetic monoepoxides is presumably a racemic mixture, and each of them has another double bond available for reaction. As a first approximation it may be assumed that the epoxidation of the second double bond is an event which is completely independent of the epoxidation of the first. It will be seen that this is not quantitatively true, but qualitatively it leads to the expectation that four isomers, two sets of mirror images, are formed. The two sets, which are related as diastereoisomers, differ from each other by their relative dispositions of the oxirane oxygens (see Fig. 1). One set has both oxirane oxygens on the same side of the imaginary plane of the molecule, while the other has them on opposite sides. From a practical standpoint, then, one would expect to find two kinds of 9,10:12,13-diepoxy-stearic acid (or ester) which have somewhat different properties and are therefore potentially separable. The situation is entirely analogous to the well-known and much-studied 9,10,12,13-tetrabromostearic acid (16) which has been known for over 50 years to exist in two forms, one a solid, mp 115.3C, and the other a liquid at room temperature. It was believed for many years that the solid or " *$\alpha$* " form and the liquid " *$\beta$* " form of tetrabromostearic acids result from the bromination of two different kinds of linoleic acids, an " *$\alpha$* " and a " *$\beta$* " form. It is now recognized (17,18) that there is only one form of linoleic acid, and that the solid and liquid forms of tetrabromostearic acid are really diastereometric isomers, each of which is a racemic mixture.

Oxirane analysis of the crude product obtained on epoxidation of methyl linoleate indicated that conversion of double bonds to oxirane functions in this compound proceeded in comparable yield to the epoxidation of methyl oleate (19). Examination of the initial epoxidation product of methyl linoleate by gas-liquid chromatography (GLC) showed, that in the region where elution of methyl diepoxy-stearate is expected, there are two peaks instead of one. Similar double peaks were found in the diepoxide region when commercially epoxidized oils were transesterified

to their methyl esters and examined by GLC. In all cases, the first peak was larger than the second and the area ratio of the peaks were approximately 3:2. Trapping of material from each peak and reinjection in the chromatograph gave single peaks, indicating that the two components observed were real and not the result of changes during analysis.

Crystallization of solid methyl 9,10:12,13-diepoxy-stearate from the initial epoxidation product, recrystallization of the solid isomer, and GLC analysis of the latter gave a single peak identical in elution time with the first and larger of the double peaks of the crude. GLC analysis of the residue remaining after removal of the solid diepoxide showed a small peak attributable to residual solid isomer and a highly attenuated second peak now recognized to be due to a second isomer of methyl 9,10:12,13-diepoxy-stearate. Numerous attempts were made at further purification of the liquid isomer. Column chromatography on silica gel or Florisil, low temperature crystallization from various solvents and fractional crystallization of the corresponding carboxylic acids all were unsuccessful in decreasing the solid isomer content below the 11–14% level. A decrease in the solid isomer content was accomplished by taking advantage of the fact that the liquid isomer forms a urea complex somewhat more readily than the solid. While the monoepoxide is also enriched in the complex, this represents no problem since the monoepoxide can be separated cleanly from diepoxide by adsorption chromatography either before or after urea treatment. The effect of change in the relative amounts of urea and methanol per gram of sample on product recovery and on liquid:solid isomer ratio is shown in Table I. After the liquid isomer reached a purity of about 91–92% it was readily purified further by low temperature crystallization.

Saponification of the solid and the liquid ester gave 9,10:12,13-diepoxy-stearic acids, mp 78.1–78.5C and 40.8–41.7C, respectively. The former acid is well known, but the latter has not been reported previously. Other authors who have reported a liquid form of the ester (8–10) undoubtedly isolated a product highly contaminated with solid isomer. They reported the acid derived from the liquid ester to be liquid at room temperature.

The two methyl esters as well as their derived acids give somewhat low results when subjected to oxirane oxygen analysis, the liquid isomer and its corresponding acid being by far the worse offender in this respect (20). The most likely cause for this is the great tendency of these diepoxides to undergo acid-catalyzed rearrangement. This latter reaction will be described more fully in a subsequent paper.

In order to establish that the solid and the liquid esters both are 9,10:12,13-diepoxy-stearates the two compounds were subjected to periodic acid cleavage (21). Both esters gave identical mixtures of hexanal and methyl azelaaldehyde, as expected, in addition to by-products due to rearrangement.

TABLE I  
Methyl Diepoxy-stearate Isomers-Urea Complexes

Urea (g)	Methanol (ml)	Product recovered from complex <sup>a</sup> Wt. (g)	Liquid/solid isomers
3	20	0.14	14.0/1
3	15	0.29	14.5/1
3	10	0.60	12.0/1
6	20	0.65	8.5/1
9	20	0.77	8.5/1

<sup>a</sup> Starting with 1.0 g mixture, liquid/solid = 6/1.

Both the NMR and IR spectra of the two isomeric esters differ somewhat, but the interactions are so complex that any attempts to use these spectra to assign structures to the isomers would be major undertakings. Optical rotation, on the other hand, offers a convenient and rapid method of resolving the question of structural identity. Naturally occurring 12,13-epoxy-9-octadecenoic acid, vernolic acid, is optically active (22,23), although its activity is rather weak, and methyl vernolate derived from *Vernonia anthelmintica* seed oil has been reported (24) to be weakly active in ethanol solution ( $[\alpha]_D^{25} = -0.3$ ). While the methyl diepoxystearates derived from methyl linoleate were both found to be optically inactive in our laboratory the solid isomer prepared from epoxidized methyl vernolate had considerable activity ( $[\alpha]_D^{25} = -12.86$ ), and the corresponding liquid isomer had very low, but significant activity ( $[\alpha]_D^{25} = -0.77$ ). Since the latter isomer still contained about 2% of the solid as an impurity its absolute activity is probably lower than that stated above.

The optical activity data of the liquid isomer as compared with the solid indicates that the liquid contains a feature of internal compensation, a pseudoplane of symmetry. (There can, of course, be no real plane of symmetry since the ends of the molecule, though far removed from the site of chirality, are different.) The solid isomer, on the other hand, is strongly active, indicating that the symmetry feature of the liquid isomer is absent. From Figure 1, and from corresponding molecular models, it is seen that the structure having both oxirane oxygens on the same side of the imaginary molecular plane has a pseudoplane of symmetry passing through the methylene group separating the oxirane functions and therefore represents the liquid isomer, while the structure having oxirane oxygens on opposite sides must be the solid isomer.

Introduction of a second oxirane oxygen into mono-epoxidized methyl linoleate is much slower and less exothermic than the epoxidation of the first double bond of methyl linoleate or of the double bond of methyl oleate. If one follows the progress of epoxidation of methyl linoleate by GLC, then one finds that the monoepoxidation of the starting material is

essentially complete before significant amounts of diepoxide appear. Taken together, these facts indicate deactivation, probably by an inductive effect, of the second double bond by the oxirane oxygen introduced first.

On a statistical basis one would expect to obtain equal amounts of the two isomeric diepoxides. Since under normal epoxidation conditions the solid isomer (oxygen on opposite sides) is always formed in excess, it must be concluded that there is a slight energy barrier favoring approach of the epoxidizing agent on the side opposite to the one holding the first oxirane oxygen. It is doubtful that this is a simple physical blocking effect, since use of a bulkier epoxidizing agent, *m*-chloroperbenzoic acid, did not influence the ratio of isomers produced.

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